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A model-based and a multi-objective optimisation framework for incremental scale-up of bioreactors

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Scale-up is an important stage in development and commercialization of new process technologies in many industries, for production of chemicals such enzymes, antibiotics or materials such as bioplastics. Moving a fermentation process from a lab-scale to a commercial/production scale remains still challenging due to a number of factors that affects biological response of cells to changing conditions from cultivation. Scale-up problems may arise then due to inadequate interphase mass transfer, heat removal and non-uniform temperature and concentration gradients in the reactor (Villadsen et al. 2011). As a result, many large-scale fermentation processes give a lower yield than achieved in the laboratory.

Traditionally, scale-up problem is tackled using a step-wise process development approach: from lab-scale to pilot-scale and ultimately to production-scale by following certain empirical criteria based on dimensionless numbers or ratios critical to performance of the process. The difficulty with this approach lies in several aspects as there is just a limited number of empirical criteria than one can keep constant during the scale-up. Additionally, the controlling conditions (bottleneck) may change at different scales.

This contribution aims at developing a framework for scale-up of bioreactors based on data and information translated into quantitative knowledge using models. The framework allows using multiobjective scale-up principles and various degree of models, from first-principles to empirical (e.g. response surface type models based on experimental data) to hybrid models.

The proposed methodology is illustrated as a flowchart in Figure 1 and assumes that a successful bioreactor design and operation protocol has been developed at a lab/bench scale. The methodology consists of the following steps:

1) **Definition of objectives and constraints**: where the objective of the scaled-up operation is defined, including the scaling-up factor. It is important to note that the goal of scaling-up is not to reproduce the bench scale reactor at a larger scale but to accomplish the objective defined. To this aim, the bioreactor configuration can be modified in the large scale

2) **Model development.** Depending on the available information and the goal of the process, a model with the corresponding assumptions is formulated at the small scale and is assumed to be translatable to the large scale. The model complexity can range from complete first-principle model including the mass, heat and momentum balances and a structured metabolic kinetic description to simple meta-models, e.g. obtained from an experimental campaign response surface methodology.

3) **Design scale-up.** Using the model developed, the problem of design at a large scale is formulated as an optimization to achieve the defined objective. If a full model is available, the large scale design can be done without taking into account the bench scale protocol. Otherwise, sensitivity analysis of the bench scale model is used to determine the operating parameters that affect most the performance of the reactor. In the vast majority of cases the scale-up will represent a trade-off since not all the operation parameters/ratios can be kept constant. A multiobjective optimization is proposed as a systematic method to carry out the scale up, hence keeping constant the most significant operating conditions and parameters (according to the sensitivity analysis) and whereas the least important ones can be varied. Hence, the use of multiobjective optimization together with an assessment of the model in order to choose the most relevant phenomena for the process provides a rational method for scale-up.

4) **Scale-up validation**. The goal of this step is to check whether the assumptions formulated in step 2 are applicable at the new scale and thereby, the validity of the model and the scale-up. The most spread and straightforward tool is the regime analysis of all the phenomena taking place in the reactor. The limiting steps can be therefore inferred and, the hypotheses used to build the model can be validated (Sweere et al. 1986). Otherwise, a more complex model is needed in order to properly describe the operation in the reactor, and the hypotheses are reformulated.

5) **Evaluation**. This step consists on checking whether the objectives initially defined are actually fulfilled at the large scale. If not, the model and/or the objectives may have to be redefined if the model cannot capture the bioreactor description properly or if the defined objectives are not feasible at large scale.

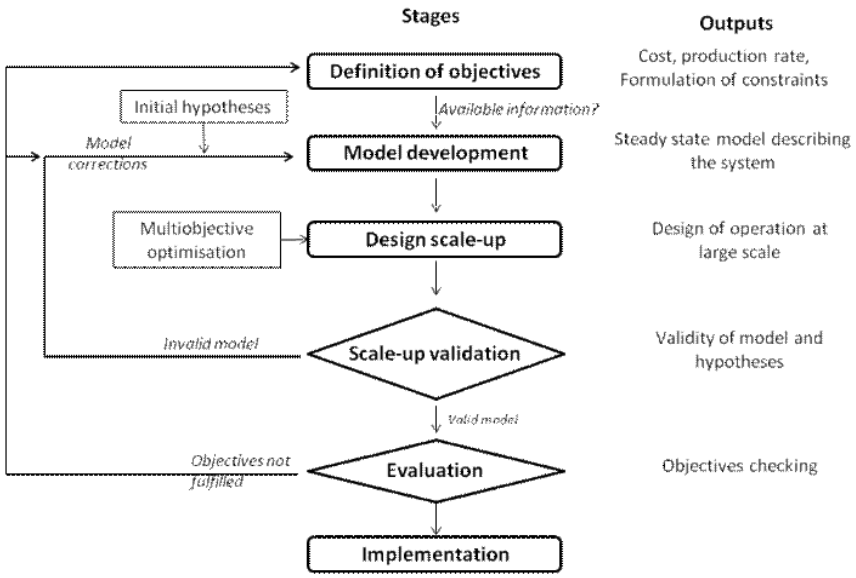

Figure 1. Methodology proposed for incremental scale-up of bioreactors based on incremental model development

The methodology is illustrated step by step through a case-study consisting on a bacterial fermentation scale-up (*E. coli* in a rich glucose environment, Villadsen et al. 2011) assuming different levels of available information: i) a full model, ii) a partial model consisting on mass balances and kinetic rates but failing to include hydrodynamics and iii) a meta-model obtained from simulated experimental data. The results using the methodology were benchmarked with other widely used methods based on rules of thumbs (e.g. keeping the power/volume ratio constant at all scales) and dimensional analysis (e.g. keeping the Sherwood number constant at all the scales). The proposed methodology was proven to provide a rational framework for scaling up, considering both simple and complex models.

References

Villadsen J. et al. (2011) *Bioreaction Engineering Principles.* Springer Science

Sweere, A.P.J. Luyben, K.C.A. M., Kossen, N.W.F.. (1986), Regime analysis and scale-down: tools to investigate the performance of bioreactors, *Enwyme Microb. Technol. vol.9, 386*

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